Digestive and Liver Disease xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Hepatic arterial infusion in the management of colorectal cancer liver metastasis: Current and future perspectives

Nicolas Chapelle[a,b,*], Tamara Matysiak-Budnik[a,b], Frédéric Douane[c], Sylvie Metairie[d], Philippe Rougier[b], Yann Touchefeu[b]

[a] University of Nantes, Nantes, France
[b] Nantes University Hospital, Hôtel-Dieu, Digestive Disease Institute, Gastro-Enterology, Hepatology and Digestive Oncology Unit, France
[c] Nantes University Hospital, Radiology Unit, France
[d] Nantes University Hospital, Digestive Surgery Unit, France

ARTICLE INFO

Article history:
Received 12 August 2017
Received in revised form 4 December 2017
Accepted 6 December 2017
Available online xxx

Keywords:
Colorectal neoplasms
Hepatic artery infusion
Liver metastases
Oxaliplatin

ABSTRACT

The technique of hepatic arterial infusion (HAI) for the treatment of liver metastases from colorectal cancer has been developed over more than 30 years. Although the indications and protocols for this technique have evolved with time, HAI is not routinely performed in clinical practice. Studies have been heterogeneous, with different regimens of intra-arterial drugs, associated or not with systemic chemotherapy, and with unconvincing outcomes. Technical difficulties for catheter placement have limited the implementation of this method in routine practice. The aim of this review is to present recent studies, highlighting technical improvements and promising combinations of oxaliplatin-based HAI with systemic treatments. HAI is being investigated in both the metastatic setting – in the first line and beyond – and in the adjuvant setting, and we will discuss its potential place in current and future patient management.

1. Introduction

Overall, 30–60% of patients with colorectal cancer (CRC) will develop exclusive or predominant liver metastases (LM) [1,2]. These LM are synchronous in 25% of cases, and curative surgery or thermoablative treatments are possible in only 10–15% of patients. Five-year overall survival (OS) in metastatic CRC (mCRC) remains low, around 20% in recent studies [3]. However, the development of systemic combinations of chemotherapies and monoclonal antibodies has been associated with an improved OS, and this also allows an increased rate of secondary resections of LM in 10–30% [4–6]. Complete resection of LM is associated with an increase in five-year OS to 50–80% and disease-free survival (DFS) to 10–20%. HAI was developed more than 30 years ago, associated with increased local responses of LM, and in a few studies with increased OS [7,8]. More recently, and in specific conditions, it has been shown that HAI may make possible a secondary resection with curative intent in selected patients. The aim of this article is to review current and future indications of HAI in the management of mCRC.

2. Biologic rationale

The vascular supply to the liver normally derives 70% from the portal vein and 30% from hepatic arteries, while early-stage tumor lesions are mainly supplied by hepatic arteries [9–13]. Thus, the aim of HAI is to deliver therapeutic agents directly into the liver and to obtain a high drug concentration in the tumor. It has been demonstrated that pharmacokinetic characteristics after HAI of antineoplastic drugs are favorable, with high extraction ratios and local drug concentrations. In a rabbit model, oxaliplatin HAI was associated with a higher hepatic drug concentration compared with cisplatin HAI, and higher hepatic drug concentrations compared with those achieved by systemic oxaliplatin administration, suggesting a favorable pharmacokinetic profile of oxaliplatin HAI [14–17] (Table 1). Floxuridine (FUDR) and 5-fluorouracil (5-FU) have short serum half-lives, and are catabolized by liver enzyme systems. Hepatic drug extraction has been studied for more than 40 years, calculating the difference between the amount of drug infused into the hepatic arterial catheter and the total drug effluent measured in the hepatic vein. With FUDR, 94–99% of the drug is extracted in the liver, with systemic levels approximately 25%

* Corresponding author at: Institut des Maladies de l'Appareil Digestif, Gastrointestinal Oncology Unit, University Hospital, 1 place Alexis Ricordeau, 44093 Nantes Cedex 1, France.
E-mail address: nicolas.chapelle@chu-nantes.fr (N. Chapelle).

https://doi.org/10.1016/j.dld.2017.12.004
1590-8658/

Table 1
Intra-arterial/intravenous tumor concentration ratio of the main drugs used in digestive oncology.

Drugs	Intra arterial/intravenous tumor concentration ratio
FUDR [17]	100–400
PIRARUBICINE [15]	20
5FU [18]	10
Mitomycin C [16]	6–8
Cisplatin	4–7
Oxaliplatine [14]	5

of those obtained with peripheral venous infusion. With 5-FU, systemic levels obtained with HAI range from 50% to 77% of corresponding levels obtained with peripheral venous infusion. These drugs with high hepatic extraction rates are good candidates for an HAI regimen [18]. In Europe, FUDR is seldom used, because of its intra- and extrahepatic biliary toxicity, and it is replaced by 5-FU, with a more easily manageable toxicity [8,19]. Irinotecan is a prodrug that is hydrolyzed to its active component, SN-38 (7-ethyl-10-hydroxy-campthotecine) by hepatic carboxylesterases. The hepatic carboxylesterase isoforms have a low affinity for irinotecan, and there is a preferential intratumoral activation due to a higher carboxylesterase activity in CRC cells. Recent studies have found increased biliary toxicity when bevacizumab is used concomitantly with FUDR, without benefit on progression-free survival (PFS) or OS. Thus, this drug association is no longer recommended [20,21]. When used in HAI, oxaliplatin seems to have the same toxicity profile as intravenously [22].

3. Intra-arterial and systemic combinations of unresectable LM

A concomitant use of systemic and intrahepatic chemotherapies has been developed recently, initially with systemic LV5-FU alone [23]. Subsequently, with the development of systemic polychemotherapy, improved outcomes have been reported. For example, increased tumor response rates, up to 80%, have been described with a strategy associating HAI-FUDR with IV drugs (irinotecan/5-FU/oxaliplatin or oxaliplatin/irinotecan) [24,25]. In selected patients, these combinations have led to 80% response rates as a first-line treatment and 50% as a second-line treatment. In the USA, a systemic combination of FUDR-irinotecan with HAI-oxaliplatin has shown a 90% response rate, with a 50% secondary resection rate [24]. HAI with oxaliplatin has been developed for more than 15 years, mostly in Europe. The major studies are presented in Table 2 [26–35].

Recent studies have investigated the combination of doublet or triplet HAI chemotherapy regimens [30,31]. A recent French multicentric, prospective, phase II trial (OPTILIV) investigated a triplet chemotherapy by HAI (oxaliplatin/5-FU/irinotecan) combined with systemic cetuximab in patients with unresectable RAS-wild-type LM of CRC, after a first-line systemic treatment. Tolerance was acceptable and tumor responses (40.6% response rate) allowed a R0-R1 secondary resection in 29.7% of cases. Median PFS was 9.3 months. OS was increased two-fold in patients who underwent resection compared with those without resection (35.2 months vs. 18.7 months, respectively). Forty-five percent of secondary-resected patients were still alive after four years, compared to none in the non-resected group [33]. In a recent meta-analysis including patients treated with systemic FOLFOXIRI plus bevacizumab in the first line, the secondary resection rate was 40% (28% R0), and PFS and OS were 12.4 and 30.2 months, respectively [6]. Intensive systemic and HAI strategies must be compared in randomized clinical trials.

To demonstrate the additional benefit of HAI combined with IV chemotherapy, a prospective phase III study has been launched comparing oxaliplatin administered by HAI versus IV in association with systemic LV5FU2 and bevacizumab or panitumumab (according to molecular tumor profile) in the first-line treatment of patients with unresectable LM (FFCD PRODIGE 49 OSCAR trial). However, more studies are needed to validate the best combinations of HAI with systemic therapies in terms of efficacy and safety.

4. Adjuvant hepatic arterial infusion in patients at high risk of recurrence

After curative resection of CRC LM, the risk of relapse ranges from 30% to 90%, and half of these patients will develop LM exclusively [36]. Several studies have evaluated the role of HAI as an adjuvant treatment to reduce LM recurrence [37]. A randomized trial demonstrated increased disease-free survival in a group treated with systemic chemotherapy (5-FU) plus HAI (FUDR) compared with those treated with systemic chemotherapy alone (37.4 versus 17.2 months, $p < 0.01$) [38]. However, a meta-analysis of two randomized controlled trials investigating adjuvant 5-FU-based systemic chemotherapies did not demonstrate an improved OS [39].

A recently published monocentric cohort included 2368 consecutive patients with complete resection of CRC LM. Of these, 785 patients received FUDR HAI in association with systemic therapy. HAI was perioperative (79 patients), preoperative (53 patients), or adjuvant (653 patients). Five-year OS was significantly higher in patients treated with HAI versus without HAI (52.9% versus 37.9%, respectively, $p < 0.001$). The ten-year OS of patients treated with HAI versus without HAI were 38.0 and 23.8%, respectively ($p < 0.001$) [40]. A French retrospective study included 98 patients who had undergone curative resection of at least four LM. Forty-four patients (45%) received post-operative oxaliplatin HAI in combination with systemic 5-FU, while the remaining patients received systemic chemotherapy alone. There was a strong benefit for disease-free survival in the HAI group (HR: 0.37 (95% CI: 0.23–0.60); $p < 0.0001$), but no significant effect on OS [41]. A randomized clinical trial is ongoing, comparing oxaliplatin HAI combined with systemic LV-5-FU with systemic FOLFOX regimen in patients with at least four resected or thermoablated LM (PACHA 01 trial, UNICANCER).

5. Technical considerations and catheter-related complications

Port-catheters can be surgically implanted, or placed percutaneously. In the surgical technique, the catheter is implanted during a laparotomy, usually when the primary tumor is being removed. This method allows surgical exploration of the whole abdominal cavity, prophylactic ligature of arteries to avoid extrahepatic infusions, prophylactic cholecystectomy (to prevent chemical cholecystis), and perioperative control of the infusion quality of injection through the catheter by injecting blue or fluorescein. In the radiological technique, a percutaneous radiologic placement is performed through the femoral artery. The catheter tip can be placed in the gastroduodenal artery, which is then embolized. The catheter is perforated with a side hole placed to enable the infusion into the hepatic artery. The catheter is connected to a subcutaneous port to allow easy access and repeated administrations after a control arteriography [42]. According to retrospective studies, there is no significant difference between surgical or radiologic implantation in terms of efficiency and local complication rates [43]. However, due to its simplicity and a trend for a longer catheter life and lower rate of complications after radiologic implantation,

Please cite this article in press as: Chapelle N, et al. Hepatic arterial infusion in the management of colorectal cancer liver metastasis: Current and future perspectives. Dig Liver Dis (2017), https://doi.org/10.1016/j.dld.2017.12.004